Inflammation and Atherosclerosis

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Atherosclerosis

A pathological process that causes:

• Coronary artery disease
  – Angina pectoris
  – Myocardial infarction
• Cerebrovascular disease
  – Ischemic stroke
  – Vascular dementia
• Peripheral vascular disease
  – Gangrene

Risk factors:

  High plasma cholesterol
  High blood pressure
  Smoking
  Diabetes
  Inflammation
Atherosclerosis is an inflammatory disease

- **Immune activity in plaque**
  - T cells, Macrophages
  - HLA, costimulatory factors, and cytokines

- **Systemic response**
  - CRP, IL-6, Antibodies

- **Genetic association**
  - Alleles of immune and inflammatory genes

- **Immunopathogenesis**
  - Major effects of immune factors in model organisms

*HLA-DR in human plaque*  
Jonasson & Hansson 1985
Inflammation in coronary arteries leads to release of inflammatory mediators into circulation - and triggers acute phase reaction in liver

GK Hansson
Inflammation (Latin, inflammare, to set on fire) is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.

A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.
Inflammation is typically triggered when bacterial pathogens invade the organism.
Inflammation

Hansson-Libby-Schönbeck-Yan, Circ Res 2002
Toll-like receptors recognizing pathogen molecules trigger inflammation

Lundberg & Hansson, Clin Immunol 2010
Toll-like receptors can also recognize danger-associated endogenous molecules

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Function</th>
<th>TLR</th>
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<tbody>
<tr>
<td>Hsp60</td>
<td>Stress inducible cytosolic heat shock protein</td>
<td>TLR2/TLR4</td>
</tr>
<tr>
<td>Hsp70</td>
<td>Stress inducible cytosolic heat shock protein</td>
<td>TLR2/TLR4</td>
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<tr>
<td>Gp96</td>
<td>Stress inducible ER heat shock protein</td>
<td>TLR2/TLR4</td>
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<td>HMGB1</td>
<td>Chromosomal binding protein</td>
<td>TLR2/TLR4</td>
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<tr>
<td>ApoCIII mRNA</td>
<td>Apolipoprotein in VLDL</td>
<td>TLR2/TLR3</td>
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<tr>
<td>Fibrinogen</td>
<td>Acute-phase protein</td>
<td>TLR4/TLR4</td>
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<tr>
<td>Fibronectin EDA</td>
<td>ECM component</td>
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<tr>
<td>Heparan sulfate</td>
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<td>Hyaluronan fragment</td>
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<td>β-defensin 2</td>
<td>Cationic antimicrobial peptide</td>
<td>TLR4/TLR4</td>
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<tr>
<td>Oxidised phospholipid</td>
<td>Component of oxLDL</td>
<td>TLR4/TLR4</td>
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<tr>
<td>mmLDL</td>
<td>Lipoprotein modified by mild oxidation</td>
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<tr>
<td>Nucleic acids</td>
<td>RNA/DNA-containing immune complex</td>
<td>TLR7/TLR9</td>
</tr>
</tbody>
</table>

*Lundberg & Hansson, Clin Immunol 2010*
Innate immune response of macrophages is initiated by cholesterol crystals that activate the inflamasome

Duewell Nature 2010
Rajamäki PLoS One 2010

Hansson & Hermansson, Nature Immunol 2011
The activated T cell can instruct the B cell to make antibodies to its cognate antigen, and activate the macrophage to promote inflammation.
Two types of immunity

**Innate**
- Macrophages, EC and other cells
- Receptors are germ-line encoded
- Broad specificities
- Modest affinities
- Rapid
- Stupid (= no memory)

**Adaptive**
- T and B cells
- Receptors generated by somatic rearrangement
- MHC restriction
- High specificity and affinity
- Slow
- Clever - memory
Macrophages and T cells accumulate at sites of LDL retention in the forming atherosclerotic plaque

Libby, Ridker & Hansson, Nature 2011
The atherosclerotic plaque – a site of immune inflammation

Hansson & Hermansson
Nature Immunol 2011
Lack of IL-1β or NLRP3 inflammasome of innate immunity dramatically reduces atherosclerosis

*Duewell et al, Nature 2010*
Lack of adaptive immunity leads to dramatic reduction in atherosclerosis

**Aortic lesion size**

- **Apoe**
  - **Yes**
  - **No**

**T and B cells**

- **Yes**
- **No**

*Zhou et al, Circ 2000*
INFLAMMATION, ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE
State-of-the-art for atherosclerosis

• The disease process is an inflammation triggered by LDL accumulation
• Inflammation is an independent risk factor
• Current markers (hsCRP) are informative – their use in screening debated
• Antiinflammatory therapies should be evaluated for effects on CVD
  • TNF blockers / RA; methotrexate; statins
Innate and adaptive immune reactions cause progression of atherosclerosis

Mediators of cardiovascular inflammation

- Proinflammatory immune cytokines
  - IL-1β, IL-18, TNF, Lymphotoxin, Interferon-γ
- Cell surface molecules of immune cells
  - CD40-CD40L; CD137-CD137L; OX40L-OX40; LIGHT-LTβR
- Eicosanoids
  - Prostaglandins
  - Leukotrienes
Vascular effects of cytokines

• Interferon-γ
  • Activate EC / MHC, LAM
  • Inhibit SMC prolif, α-actin; collagen
  • Promote MMPs, iNOS

• TNF superfamily
  • Activate EC / LAM, permeability
  • Promote MMPs, NOS
  • Cytotox (esp w IFN-γ)
  • Regulate lipid metabolism (TNF - LPL, LIGHT - HL)
  • Regulate mineralization (RANKL)
Therapeutic opportunities

Plaque rupture and thrombosis

Micrographs: E Falk

GK Hansson
N Engl JMed 2005
Challenges in translating the biology of atherosclerosis to the clinic

- Animal models have provided detailed information about pathogenesis and novel principles for therapy.
- But animal models, although needed, are not perfect mimicks of human disease.
- Animal models are well suited for studying initiation and progression of atherosclerosis.
- But we lack models for plaque activation and atherothrombosis.
Challenges in translating the biology of atherosclerosis to the clinic

• Genomics has provided therapy targets and validation but limited fundamental novel information

• Atherosclerosis seems to depend on gene-environment interactions with a large number of genes, each of which makes a small contribution
Progress in translating the biology of atherosclerosis to the clinic

• Humanize mouse models
  • Lipoproteins, HLA etc

• Model plaque activation, rupture, thrombosis

• Develop better biomarkers
  • Proximal immune mediators; plaque components

• Use imaging to monitor human disease
  • High-resolution anatomic; molecular imaging

• Biobank patients
  • DNA; Patological tissue: mRNA-protein-metabolites

• Clinical trials as a laboratory for discovery
• P Libby, PM Ridker, GK Hansson, Nature , May 19, 2011
Cardiovascular Research Laboratory
Center for Molecular Medicine, Karolinska Institutet

Funding:
Vetenskapsrådet
Hjärt-Lungfonden
Stiftelsen för Strategisk Forskning
Vinnova
European Union
Leducq Foundation